

Bacterial Infections in Paediatric Patients with Chemotherapy Induced Neutropenia

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Abstract

Objective: To determine the pattern of bacterial infections, isolate and identify the pathogenic bacteria and their sensitivity to different antibiotics during febrile episodes in paediatric patients with chemotherapy induced neutropenia from January to June 2000 at the Paediatric Oncology Unit of Combined Military Hospital, Rawalpindi (CMH RWP).

Patients and Methods: The study material comprised of 62 febrile episodes occurring in 50 neutropenic children aged less than 12 years with various malignancies. All the episodes were worked up in detail including history, physical examination and relevant investigations.

Results: Total 29 bacteria were cultured in 62 febrile episodes. Fifty five percent organisms were isolated from blood and 45% from other sites, 15 (51.7%) were Gram-positive and 14 (48.3%) were Gram-negative. *S. aureus* was the most frequent Gram positive isolate and *E. coli* was the most common Gram negative isolate. The standard empiric antibiotic regimens for (combination of amikacin and ceftazidime) showed an overall response rate of 61.3%. The infection related mortality in this series was 22%.

Conclusion: Fever is the commonest symptom of infection in neutropenic children with malignancy and demands an urgent empirical antibiotic therapy after the onset of fever. Based on this study we recommend a combination of ceftazidime and amikacin for use as empiric antibiotic therapy in these children (JPMA 54:237;2004).

Introduction

Paediatric patients in oncology units are subject to severe and at times lethal infections. Breaks in epithelial barriers, interference with immune functions, malnutrition, repetitive therapeutic interventions and involvement of the haematopoietic and lymphoid system by the malignant disease process itself,¹ increase the likelihood of infection. Neutrophils are the major cellular defense against most bacteria and chemotherapy induced neutropenia is well-known to be associated with infections that may be life-threatening, particularly if not treated immediately.²

Febrile neutropenia (FN) occurs with common chemotherapy regimens in 25 to 40% of treatment-naïve patients, and its severity depends on the dose and intensity of the chemotherapy regimen, the patient's prior history of either radiation therapy or use of cytotoxic treatment, and comorbidities.³ Neutropenic fever is an oncologic emergency that requires prompt assessment and treatment with antibiotics.⁴ The risk of infection in neutropenic patients increases rapidly

when granulocytic count drops to <500 cells/mm³. The majority of severe infections are observed when granulocyte counts are <100 cells/mm³.

The spectrum of bacterial isolate has changed considerably over the past four decades.⁵ In a review of various studies by European Organization for Research and Treatment of Cancer (EORTC) it has been shown that the pattern of micro-organisms isolated changes almost every 2-3 years. Hence it is advisable to study the pattern of infections and causative organisms at an interval of 2-3 years.⁶

Keeping in view this changing pattern of bacterial pathogens and their sensitivity patterns to antibiotics we planned a study to determine the pattern of bacterial infections, isolate and identify the pathogenic bacteria and their sensitivity to different antibiotics during febrile episodes in paediatric patients with chemotherapy induced neutropenia.

Patients and Methods

The study was carried out at the paediatric oncology unit of Combined Military Hospital (CMH), in

collaboration with Department of Microbiology and Haematology at Armed Forces Institute of Pathology (AFIP) Rawalpindi, from January to June 2000. Children less than twelve years of age for the purpose of anticancer therapy who met the following criteria were included in the study:

1. Neutropenia; Absolute Neutrophil Count (ANC) less than $500/\text{mm}^3$ or a falling count anticipated to get less than $500/\text{mm}^3$.
2. Fever defined as a single oral temperature of 38.3°C or a persistent fever (temperature reading of 38°C on at least three consecutive evaluations (at > 4 hours intervals) within 24 hours period, not associated with an obvious non-infectious cause.

The following cases with fever were excluded from study:

1. Those who developed fever within 24 hours after administration of chemotherapy and the fever subsided within next 24 hours after completion of chemotherapy.
2. Fever occurring during or within 6 hours of transfusion of blood, blood products and other intravenous fluids.

All patients underwent a detailed history, complete physical examination, and relevant hematological, microbiological and radiological investigations. Urine culture and at least two sets of blood cultures were obtained. All possible sources of infection were investigated. As per protocol, every neutropenic patient was administered intravenous antibiotics, if and when they developed fever. Antibiotics were started usually within two hours of fever, after collecting specimens for cultures and other tests. Generally a combination of an aminoglycoside (amikacin) and a 3rd generation cephalosporin (ceftazidime) was used in about 80% of cases and in the rest miscellaneous antibiotics or a combination of antibiotics was used.

When the patient became afebrile by day 3, antibiotic therapy was stopped after another 48 hours if the neutrophil count was $500/\text{mm}^3$ for two consecutive days, there was no definite site of infection, and cultures were negative. Antibiotics were continued for five more days after patients became afebrile if the neutrophil count was $<500/\text{mm}^3$ on day seven of antibiotics. When there was no response to the initial empiric antibiotic therapy after 72 hours; a thorough reassessment of the patient was made. This included a complete physical examination, chest radiography, and additional cultures from blood, vascular catheters, other specimens from suspected sites of infection, and ultrasonography of abdomen to rule out any hidden abscess. The empiric anti-

otics were continued or changed according to sensitivity results or additional antibiotic was added to them. When fever persisted after seven days of initiation of therapy and the patient was still neutropenic an antifungal agent, Amphotericin B was added to the antibiotic regimen.

Collection of Clinical Specimens

1. K2 EDTA blood sample; 3.0 ml blood was collected in di-potassium salt of ethylene diamine tetracetic acid (K2 EDTA) by a clean venepuncture to perform complete blood count and when indicated to examine for haemoparasites. The samples were processed within two hours.
2. Blood for culture. Under strict aseptic measures, two sets of 2 ml of blood were collected at one hour interval on upswing of fever spike, before the start of antimicrobial therapy. Immediately after collection, the blood was added to bottles containing 20 ml brain-heart infusion broth. These were transported to department of microbiology, AFIP Rawalpindi where they were incubated at 37°C overnight. The next day subcultures were made from the broth into Blood Agar and macConkey medium and were incubated at 37°C overnight. In cases where septicemia was suspected to be due to anaerobic bacteria, an additional 9 ml of blood was collected and added to thioglycolate broth. The samples were kept at room temperature until transported to the laboratory.
3. Throat swab for culture; Throat swab was collected by a medical officer (or experienced nurse), preferably before start of antibiotic therapy or antiseptic mouth wash. The swab was delivered to the laboratory within 2 hours.
4. Pus swabs, pus, exudates; The specimens were collected from locally infected lesions (skin, wound, ulcers, ear, eyes, sinuses and deep sepsis). These specimens were collected either with sterile disposable syringes or on sterile cotton wool swabs and delivered to the laboratory within two hours of collection.
5. Urine for culture. Mid stream urine (MSU) was collected in a sterile, dry, wide necked, leak proof container and delivered to the laboratory as soon as possible. If a delay in delivery of more than one hour was inevitable, the specimen was refrigerated.
6. Stool for culture; Stool for microbiological examination was collected during the acute stage of diarrhoea. 1-2 ml of specimen was obtained (from stool passed into a clean, dry, disinfectant free bed pan or a suitable wide-necked container, unmixed with urine) into a 25 ml screw capped, wide-mouthed glass bottle and transmitted quickly to the laboratory. If a delay was unavoidable the stool were collected in 6 ml buffered glycerol saline transport medium.

7. Effusion (peritoneal, pleural etc.) fluid for routine examination (RE) and culture; Fluids were aspirated under strict aseptic precautions and transported to the laboratory within two hours.

(56.2%) Gram-positive organisms and 7 (43.8%) Gram-negative isolates. Out of 13 bacteria cultured from other sites, 6 (46.1%) were Gram-positive and 7 (53.8%) were Gram-negative isolates (Table 3).

Table 1. Diagnosis and infection related mortality of patients in paediatric oncology unit at CMH Rawalpindi.

Primary diagnosis	Patients		Mortality	
	No.	%	No.	%
Acute Lymphoblastic Leukemia (ALL)	22	44	4	18
Acute Myeloid Leukemia (AML)	4	8	2	50
Neuroblastoma	7	14	1	14.3
Wilms' Tumour	7	14	2	28.6
Non- Hodgkin Lymphoma (NHL)	3	6	1	33.3
Hodgkin's disease	1	2	00	00
Rhabdomyosarcoma	2	4	00	00
Ewing Sarcoma	2	4	00	00
Sarcoma abdomen (Non-Rhabdomyosarcoma)	1	2	00	00
Hepatoblastoma	1	2	1	100
Total	50	100	11	22

8. Cerebrospinal fluid (CSF) for routine examination and culture: In patients having meningismus or unusual lethargy CSF was collected only by an experienced medical officer under rigorous aseptic precautions in a set of two freshly supplied screw capped containers or sterile disposable syringes and transported to the laboratory within one hour of collection.

Results

During the study period 62 episodes of fever occurred in 50 neutropenic patients. Acute lymphoblastic leukemia (ALL) was the commonest malignancy constituting 44% of all cases (Table 1). There were 26 (52%) male and 24 (48%) female patients, with a mean age of 4.6 years, (range 12 months - 12 years). Six patients (12%) had two separate febrile episodes, 3 (6%) had three and 01 (2%) had four febrile episodes on separate occasions. Fever was the commonest symptom followed by pallor, vomiting, mucositis and cough (Table 2).

Total 29 bacteria, 16 (55%) from blood and 13 (45%) from other sites were isolated, 15 (51.7%) were Gram-positive and 14 (48.3%) Gram-negative. Bacteraemia was responsible for fever in 25.8% (16/62) episodes, with 9

Table 2. Clinical features of patients having febrile neutropenia (n=62).

Clinical features	No.	Percentage
Fever	62	100
Pallor	40	65
Vomiting	37	60
Mucositis	26	42
Cough	22	36
Oral ulcers	20	32
Dysphagia	9	14
Abdominal pain	7	11
Arthralgia	7	11
Rhinorrhea	5	8
Dyspnea	5	8

In vitro sensitivity tests of Gram positive cocci showed that 86.6 % were sensitive to cefotaxime, 90.9% to amikacin, 93.3% to ceftazidime, ofloxacin and ciprofloxacin, and 100% were sensitive to vancomycin. Overall 73.3% were resistant to penicillin and ampicillin, 53.3% to gentamicin, 40% to cephradine, 13.3% to cefotaxime, 9.1% to

Table 3. Bacterial Pathogens and culture sites in neutropenic patients (n=29)

Gram-Positive Organism	Blood Tip	Canuula	Pus	Throat	C SF	Stool	Urine	Total	% of Gram +ve	% of total
Staphylococcus aureus	5	2						7	46.7	24.1
Coagulase negative staphylococci	1		1					2	13.3	6.9
Streptococcus group D	1		1					2	13.3	6.9
Streptococcus pneumoniae	1			1				2	13.3	6.9
Streptococcus pyogenes	1			1				2	13.3	6.9
Gram-Negative Organism									% of Gram -ve	% of total
Pseudomonas aeruginosa	2		1					3	28.6	13.8
Klebsiella pneumoniae	2	1						3	21.4	10.3
Escherichia coli	1					1	2	4	21.4	10.3
Salmonella typhi	1					1		2	14.3	6.9
Niesseria meningitidis	1				1			2	14.3	6.9
Total	16	3	3	2	1	2	2	29		
Percentage	55.2	10.3	10.3	6.9	3.4	6.9	6.9	100		100

CSF; Cerebrospinal fluid. Gm; Gram

in approximately 60-80% of the microbiologically proven infections, with *P. aeruginosa* being a leading iso- antibiotics may be limited by special circumstances, such as drug allergy or organ (e.g., renal or hepatic) dysfunction.¹³

aminoglycosides maximum resistance was seen for gentamicin (90.9%) whereas 75% were sensitive to amikacin. In the third generation cephalosporin group, 75% of the isolates were sensitive to cefoperazone, 64.2% to ceftazidime and 57.1% were sensitive to cefotaxime. As regards to fluoroquinolones maximum number of isolates (92.8%) were sensitive to ofloxacin/ciprofloxacin. All the isolates were also tested against aztreonam and 75% showed sensitivity. The overall sensitivity of all 29 isolates showed 93.1% were sensitive to ciprofloxacin, 82.6% to amikacin, 75.8% to ceftazidime and 72.5% to cefotaxime. The resistance pattern showed that 75.8% were resistant to ampicillin and 70.3 were resistant to gentamicin (Table 4).

The results of in vitro sensitivity tests showed that all *S. aureus* were sensitive to amikacin, ceftazidime, cefotaxime, ciprofloxacin and vancomycin, whereas all were resistant to ampicillin, 42.8 % to cloxacillin and 28.5% to gentacin. The resistance pattern of *E. coli* showed 100% resistance to gentacin, 75% to ampicillin and piperacillin, and 25% to amikacin, cefotaxime and ciprofloxacin and aztreonam. *P. aeruginosa* were 100% sensitive to amikacin, cefoperazone and ciprofloxacin and 66.7% sensitive to piperacillin and ceftazidime, cefotaxime (Table 4).

Amongst the 62 febrile episodes, there was a prompt response to institution of broad spectrum antibiotics in 38/62 (61.3%) patients. In 6 (9.7%) patients vancomycin was added because the fever persisted for more than seventy two hours and cultures were unrevealing.

Gram-negative septicemia was the commonest cause of death. Three patients died of excessive bleeding and septicemia; two had pneumonia as cause of death. Cerebral abscess, abdominal sepsis, hepatitis and meningitis were responsible for death in one patient each. The overall mortality was 22% (Table 1).

Discussion

Infection in the neutropenic patients has remained a major clinical challenge for over three decades.⁷ Life-threatening complications due to bacterial infections have been reported in 5-10% of febrile episodes in childhood malignancies.^{8,9} In the late 1960s, 1970s and into the 1980s, aerobic Gram-negative bacilli were the predominant cause of infection in the neutropenic patient.⁷ Schimpff et al.¹⁰ has reported that aerobic Gram-negative bacilli were involved in approximately 60-80% of the microbiologically proven infections, with *P. aeruginosa* being a leading isolate and *S. aureus* was the most important gram-positive isolate. In the mid 1980s, the spectrum of bacteria causing infection began to change. A steady increase in Gram-positive infections occurred until presently, 60-70% of bacteremias with a single organism identified are caused by Gram-positive

cocci.¹¹⁻¹³ Coagulase-negative staphylococci and *S. aureus* are the predominant organisms. This change from Gram-negative to Gram-positive organisms is probably multifactorial. Important considerations towards this change include aggressive chemotherapeutic regimens that cause more severe mucositis, longer durations of neutropenia, almost uniform use of long-dwelling right-atrial catheters, use of H₂ antagonists and use of prophylactic antibacterial agents with relatively weak coverage of Gram-positive organisms.¹⁴ In addition to the change from Gram-negative isolates to Gram-positive organisms, "new" Gram-positive organisms have become important etiologies of infection.^{11,15}

In the present study 51.7% isolates were Gram-positive and 48.3% were Gram-negative. *S. aureus* was the commonest Gram positive isolate whereas the most common Gram negative isolates were *E. coli* followed by *K. pneumoniae* and *P. aeruginosa*. Mutnick et al.¹⁶ have documented *S. aureus*, *E. coli*, coagulase-negative staphylococci, *Enterococcus* spp., and *Klebsiella* spp.; the most frequently isolated pathogens out of 2042 isolates from bloodstream, respiratory, urinary, and cutaneous infections in 2000-2001 by 33 oncology centers, clinics, and hospitals in North America. These findings are consistent with our results and depict that the pattern of isolates in neutropenic patients are more or less similar in different parts of the world.

In the present study bacteraemia was responsible for fever in 25.8% episodes, predominantly caused by Gram-positive organisms (56.3%). Almost similar results have been documented from Aga Khan University (AKUH), Karachi^{17,18} and a study from Bonn, Germany.¹⁹ Burney et al.¹⁷ has reported a change in the pattern of bacterial isolates and their resistance to antibiotics over the past years and documented that 46% organisms were gram positive; while the *E. coli*, *P. aeruginosa*, *S. aureus*, *Enterococcus* and *Streptococci* were the commonly isolated organisms.

Despite extensive clinical studies since the 1970s, no single empirical therapeutic regimen for the initial treatment of febrile neutropenic patients has been recommended. The selection of a specific antibiotic regimen must depend however, on the local epidemiology, the type and sensitivity patterns of bacterial isolates in the institution as well as the experience of the physician and the kind of the patients being treated. The use of certain antibiotics may be limited by special circumstances, such as drug allergy or organ (e.g., renal or hepatic) dysfunction.¹³ Several studies have revealed no striking differences between monotherapy and multidrug combinations for empirical treatment of uncomplicated episodes of fever in neutropenic patients.²⁰⁻²² A 3rd or 4th generation cephalosporin (ceftazidime or cefepime)

(imipenem-cilastatin or meropenem) may be used successfully as monotherapy.²³⁻²⁷

In our study a combination of ceftazidime and amikacin was used as empiric antibiotic therapy with a response rate of 61.3%. We based the choice of an empiric antibiotic treatment upon the results of earlier studies done at many centers.^{17,28,29} Burney et al.¹⁷ recommend that aminoglycosides and third generation cephalosporins seem to be the antibiotics of choice for the upfront management of febrile neutropenic patients. Advantages of combination therapy are potential synergistic effects against some gram-negative bacilli and minimal emergence of drug-resistant strains during treatment.^{30,31} The major disadvantages are the lack of activity of these combinations, such as ceftazidime plus an aminoglycoside, against some Gram-positive bacteria, and the nephrotoxicity, ototoxicity, and hypokalemia associated with aminoglycoside compounds and carboxypenicillins.¹³ The most commonly used two drug therapy includes an aminoglycoside (gentamicin, tobramycin, or amikacin) with an antipseudomonal carboxypenicillin or ureidopenicillin (ticarcillin-clavulanic acid or piperacillin-tazobactam); an aminoglycoside with an antipseudomonal cephalosporin, such as cefepime or ceftazidime; and an aminoglycoside plus a carbapenem (imipenem-cilastatin or meropenem). Generally, the different 2-drug combinations yield similar results in neutropenic patients.³²⁻³⁴ We followed the policy of using combination regimens, to maximize the activity against Gram-negative organisms, a major threat causing septicemia and shock resulting in enhanced mortality, to provide coverage in the event the pathogen, proves resistant to one of the agents, to obtain a synergistic activity thus improving and prolonging the serum bactericidal activity, and to reduce the development of resistance. In the present study the response rate was 61.3%. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) has reported an overall success rate of 74%³³ with two drugs combination of ceftazidime and amikacin where as Ariffin et al.³⁴ has reported an overall success rate of 51.2% with same combination. These variations in response rate may be due to differences in the definition of response, type of patients and the type and sensitivity patterns of bacterial isolates.

Vancomycin was not included in the initial empiric antibiotic regimen in the present study because there is no overall increase in morbidity or mortality if vancomycin is withheld until it is needed, that is, until a Gram-positive organism is identified and the patient is not responding to the initial regimen.^{35,36} The EORTC National Cancer Institute of Canada study showed that vancomycin is not in general a necessary part of initial empirical antibiotic thera-

py, if it is available for subsequent treatment modifications.³⁷ At institutions at which these infections are rare, vancomycin should be routinely withheld until the results of cultures indicate the need for this antibiotic.¹³ The indications for use of vancomycin as initial empiric therapy are; the patient is known to be colonized with Methicillin (cloxacillin) resistant *S.aureus* (MRSA), is at an institution where fulminant Gram-positive infections are frequent, or is at an institution where infections with *Streptococcus viridans* are frequent or suspected.⁷

In the present study *S. aureus* were 100% resistant to ampicillin and 42.8% to cloxacillin whereas *E. coli* showed 100% resistance to gentacin, 75% to ampicillin and piperacillin. *P. aeruginosa* were 100% sensitive to amikacin, and ciprofloxacin and 66.7% sensitive to piperacillin and ceftazidime, cefotaxime.

Almost similar results have been reported by Burney et al.¹⁷; *E. coli*, *Pseudomonas* and *klebsiella* exhibited a great degree of resistance to the commonly used antibiotics. *S. aureus* and *staphylococcus epidermidis* were almost universally resistant to penicillin. From the same institute, Bhatti et al.³⁸ has reported that *E. coli* had the lowest sensitivity rate to Aztreonam. A study by Karim et al.³⁹ done in 1991 showed the nosocomial isolates of *P. aeruginosa* had a high frequency of resistance as compared to the community and 23% of *S.aureus* were sensitive to penicillin. In a study from New Delhi, India Dubey et al.⁵ has documented that 100% *P. aeruginosa*, were found to be sensitive to amikacin, ciprofloxacin, cefotaxime and piperacillin.

The infection related mortality rate among the neutropenic patients in the present study was 22%. Naqvi et al.¹⁸ has documented 22.7% mortality at AKUH, while Dubey et al.⁵ have documented that 27% children died in the study at New Delhi, India. This resemblance is due to similar isolates, antibiotic regimens and supportive care managements in these different institutes.

There were certain significant observations as 4/7 isolates of *S. aureus* were methicillin resistant but sensitive to amikacin, cefotaxime and ceftazidime. Moreover due to the smaller number of isolates such as *Salmonella* it is difficult to draw a meaningful conclusion regarding the sensitivity pattern. This observation points towards the limitations of study.

Conclusion

Fever is the commonest symptom of infection in neutropenic children with malignancy and demands an urgent empirical antibiotic therapy after the onset of fever. Based on this study we recommend a combination of ceftazidime and amikacin for use as empiric antibiotic therapy

therapy in these children and ciprofloxacin and Amikin combination as 2nd line regimen.

There is a requirement at national level to conduct such studies almost every three to four yearly basis and formulate national guidelines/therapeutic strategies for coping with changes in resistance and pathogen prevalence in this dynamic at-risk patient environment.

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